Pseudohyperkalaemia associated with hereditary spherocytosis in four members of a family

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Summary: Pseudohyperkalaemia was detected in four members of a family all of whom have hereditary spherocytosis with normal white blood cells and platelets counts. The degree of pseudohyperkalaemia was related to the time between sampling and cell separation, and inversely related to the temperature in which the sample was left to stand before cell separation. A fifth member of this family was free from both conditions. The association suggests linkage at a membrane level.

Introduction

Pseudohyperkalaemia may result from haemolysis *in vitro* as a result of faulty handling of blood samples during collection, separation, transport or storage.^{1–3} It is also seen in pathological conditions associated with high platelets and/or white cell counts in the peripheral blood including leukaemia,^{4,5} other myeloproliferative disorders,^{1,6} reactive thrombocytosis and thrombocythaemia,^{7–11} rheumatoid arthritis,¹² infectious mononucleosis¹³ and the rare condition, Kawasaki disease.¹⁴ However, the falsely high potassium (K) level in these conditions is related to the release of K by the platelets/white blood cells after clotting. Plasma K level is normal in these patients.¹⁵

A different type of pseudohyperkalaemia was first reported in 1979 by Stewart *et al.*¹⁶ and later by others,¹⁷ in individuals with normal peripheral white cells and platelet counts, occurring in families and thought to be of autosomal dominant inheritance.^{16,18} This type of pseudohyperkalaemia is due to a significant rise in K efflux from the red blood cells at low temperatures^{2,16,19,20} and was reversed by incubation at 37°C and by incubation of the cells with quinine.^{2,21} The aetiology of familial pseudohyperkalaemia was thought to be heterogeneous.² Meenaghan *et al.*¹⁹ have identified the Na⁺, K⁺-cotransport system and the passive permeability of K⁺ as the components of K⁺ flux that show an abnormal response to decreased temperature, while the Na⁺, K⁺-ATPase pump is normal. This abnormality has been described in association with a variety of conditions such as hereditary xerocytosis²² and β-thalassaemia minor.²³

We report the presence of familial pseudohyperkalaemia in a patient and three of his relatives with hereditary spherocytosis.

Case report

The index case is a 40 year old male admitted with a history of progressive shortness of breath. The suspected diagnosis was multiple pulmonary emboli, which was confirmed by multiple perfusion defects on isotope perfusion lung scan in the presence of normal lung function and a clear chest X-ray. He had a history of hereditary spherocytosis requiring a splenectomy in 1979. An emergency serum electrolytes estimation reported serum potassium > 10 mmol/l, sodium 132 mmol/l, urea 7.7 mmol/l, creatinine 132 μmol/l, the tested sample showed no evidence of frank haemolysis. His peripheral white cell count and platelet counts were normal. He was taking no medication and there was no evidence of adrenal failure, confirmed by normal serum cortisol levels. The electrolytes were estimated on two more samples and gave variable results (serum potassium 8.6 and 5.2 mmol/l). The electrocardiogram showed no features of hyperkalaemia.

Pseudohyperkalaemia was, therefore, suspected and repeat blood samples were taken to estimate the potassium level in the serum and plasma after separation of the cells immediately after sampling. Serum and plasma separation were delayed in another set of samples for 2½ hours followed by estimation of the potassium level. The results showed a normal level for potassium in both serum

and plasma from samples, which were separated immediately (4.4 and 4.3 mmol/l, respectively). However, potassium levels were raised to 8.5 and 9.1 mmol/l, respectively, when the samples were left to stand for 2½ hours before separation at room temperature. None of the samples showed evidence of haemolysis. This was supported by normal lactate dehydrogenase levels in the samples in which the potassium levels were high. A further six samples of clotted blood were tested at different times between venepuncture and analysis, the serum being separated from the cell clot just before analysis and showed progressive rise in potassium level from 4.7 mmol/l to > 10 mmol/l at 3 hours. There were no significant changes in the potassium level in the control samples with time (Table I). The effect of temperature, in which the samples were kept before the serum was separated from the clot, on the potassium level was also studied. This showed a serum potassium of 4.7 mmol/l on immediate analysis whilst that of a sample kept at room temperature for 3 hours was > 10 mmol/l. Samples kept at 4°C and 37°C for 3 hours showed serum potassium levels of > 10 mmol/l and 5.5 mmol/l, respectively. The patient's siblings and children were also studied. All the relatives with hereditary spherocytosis (none of whom had had splenectomy), as confirmed by the abnormal blood film and increased red cell fragility, also showed pseudohyperkalaemia (Table I). One of the patients' two sons was free from both hereditary spherocytosis and pseudohyperkalaemia. A local

patient with hereditary spherocytosis unrelated to the index case was also studied and showed no evidence of pseudohyperkalaemia. The findings were explained to those in whom pseudohyperkalaemia was detected and they were advised to inform any treating doctor if their blood needed to be tested in the future to avoid unnecessary and potentially harmful treatment.

Discussion

The apparent high level of potassium in the index case and three of his relatives is consistent with a familial pseudohyperkalaemia syndrome. The question that then arises is whether there is a genetic linkage between the spherocytosis and pseudohyperkalaemia. The finding of the pseudohyperkalaemia in only those members of the family also showing spherocytosis supports but does not confirm such a linkage. Pseudohyperkalaemia has been described in other forms of congenital haemolytic anaemia such as xerocytosis.²² However, since hereditary spherocytosis is not rare and pseudohyperkalaemia has not been reported with it before, the findings could be due to the chance finding of two separate conditions, both with an autosomal dominant mode of inheritance affecting one family. Unfortunately there are no further members of the family to investigate to look for possible divergence in the transmission of the two conditions.

Table I Effect of time between blood sampling and separation of cells on the level of serum potassium (samples kept at room temperature)

Subject	Base line	0.5	K (mmol/l) at time (hours)			
			1	1.5	2	3
Index case: hereditary spherocytosis splenectomy, PE	4.7	6.2	7.8	8.5	9.3	> 10
Brother: hereditary spherocytosis	4.4	5.4	6.4	7.5	8.0	9.9
Sister: hereditary spherocytosis	4.2	5.2	5.7	6.8	7.2	8.4
Son: hereditary spherocytosis	4.4	5.9	7.3	8.4	9.3	> 10
Son: no spherocytosis	4.0	4.0	4.0	4.0	4.0	4.1
Wife: normal	4.3					4.4
Unrelated: hereditary spherocytosis (male)	4.9	5.1	5.0	5.1	5.1	5.2
Normal control (male)	4.2	4.4	4.4	4.4	4.4	4.4
Normal control (male)	4.1	4.8	4.2	4.2	4.1	5.0

The increased red cell fragility in spherocytosis itself does not appear to be the cause of the pseudohyperkalaemia, otherwise it would be accompanied by evidence of haemolysis. Furthermore, red cell fragility is decreased^{2,24} rather than increased in the hereditary xerocytosis in which pseudohyperkalaemia is also described.²²

Clinicians and biochemists need to be aware of rare cases of pseudohyperkalaemia such as these so as to avoid unnecessary and potentially dangerous measures aimed at reducing what are in fact normal

in vivo levels of potassium in such individuals. We screened the family of our index case with this in mind, and those affected, and their family doctors now know the findings and their meaning.

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